Arrest of Bleeding

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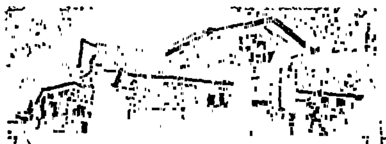
Arrest of Bleeding

PHYSIOLOGY • PHARMACOLOGY • PATHOLOGY

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Introduction

THE SPONTANEOUS arrest of hemorrhage or spontaneous hemostasis is an important chapter of homeostasis, for it is the prerequisite of the maintenance of blood in the organism.

Up until now, this phenomenon has been studied in an analytical way. Thus many facts have been discovered concerning the main factors leading to the end of bleeding, i e , coagulation of the blood, formation of a white thrombus at the mouth of vascular wounds, and contraction of the injured arteries or veins. But the respective role of these factors in the arrest of hemorrhage and their mechanism are still imperfectly known.

Our special purpose here is to give a general view of spontaneous hemostasis studied in its component parts, but mainly as a whole.

Such a study is now possible. Previously, the techniques for measuring the length of hemorrhages were unstandardized. Therefore, the bleeding time—i e., the time required for a hemorrhage to cease after a stab or cut wound of the skin—had been considered for many years highly variable and of little scientific interest. In order to be a statistically reliable test of an experimental animal or man, bleeding time must be what we call the "mean bleeding time," i.e., the average value of a sufficient number of individual bleeding times measured under standardized conditions Under these conditions, we have found the mean bleeding time to be constant in a given subject.

This led us to the statistical method for studying the arrest of hemorrhage, the results of which are presented here If the mean bleeding time has been measured at one ear and if its statistical variability is known, then the action of a physiological,

pathological or pharmacological factor on spontaneous hemostasis will result in the modification of the mean bleeding time measured at the other ear. This would be a valid test for the action of this factor on the bleeding time, provided the agent to be tested was the only one to have acted on the organism between the two series of determinations.

The present monograph is especially devoted to the facts discovered with the aid of this new statistical method.

Acknowledgments

WE ARE INDEBTED to Mr. Roger B. Goodfriend for the expert correction of the English text.

For almost thirty years our studies and those of our collaborators on blood platelets, hemorrhagic diseases and spontaneous hemostasis have been aided by the Belgian "Fondation Universitaire," "Fonds National de la Recherche Scientifique" and "Patrimoine de l'Université de Liège" The grants we received from these foundations are gratefully acknowledged

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The Analytical Study of Spontaneous Hemostasis

As ALREADY stated, effective spontaneous hemostasis is undoubtedly achieved by the combined action of at least three processes: (1) the formation of a white thrombus at the mouth of vascular wounds; (2) the coagulation of the blood, (3) the contraction of injured arteries and veins. The participation of other factors such as clot retraction or syneresis and possible vasoconstricting properties of platelet extracts is almost entirely speculative and lacks sufficient experimental evidence. Therefore, these factors will not be considered here.

THROMBUS FORMATION

When a minute vessel is cut, *bleeding is usually stopped not by coagulation, but by the formation of a white thrombus.* This white thrombus, also called hemostatic plug, results from the agglutination of the platelets to each other and to the wound of the vascular wall The removal of the platelet plug causes a renewed bleeding The role of the platelets in stanching a wound has therefore been considered an essential one It was asserted that a sufficient decrease in the platelet count always results in a prolonged bleeding time

Let us go into more detail about some of these points.

By means of snapshots and moving pictures, it has been definitely established that blood streaming out of a cut artery or vein immediately abandons platelets to the lips of the wound.[1, 2, 3, 4] This initiates a platelet plug developing not in-



Figure 1 Structure closing a vascular wound Discrepancy between the arrests of bleeding at both ends of a transected artery
A P proximal end of the transected mesenteric artery (notice the moniliform vasoconstriction), B blood still streaming out of this end, H P hemostatic plug having closed the distal end of the artery (A D) 2 min 30 sec after the cutting, V the corresponding vein
This snapshot has been taken at the 10th min of the hemorrhage

side the vessel, but in the direction of the stream, at last sealing the injured vessel not in the manner of a bottle closed by a cork, but by a capsule (see Fig. 1). The presence of fibrin strands as well as white and red cells in the hemostatic plug is not an early process nor a necessary one to stop the bleeding.

In the beginning, the whole platelet plug or parts of it are often carried away by the blood stream, but as soon as the plug or a part of it is removed, its reconstruction begins again. Although the presence of fibrin in the hemostatic plug has failed to be proved, the firmness of the latter is reduced if there is a decrease of blood coagulability. Then the plug is less adherent or allows the blood escaping from the vessel to run through channels inside it for a much longer time.

The mechanism of platelet adherence to the injured vessel wall as well as to any "wettable" foreign surface is still puzzling.

It depends upon a modification of these surfaces by plasma (or serum) proteins. This modification is identical to the modification of the surfaces of foreign bodies which leads to phagocytosis. These changes depend upon the presence in the plasma (or in the serum) of proteins which are destroyed at 56°C and have been called "natural opsonins" by the bacteriologists who studied phagocytosis. That is the reason why we also term "opsonization" the modification of a surface leading to the clumping of the blood platelets to it.

This "opsonization," and therefore the adherence of platelets, is prevented by every factor which prevents blood coagulation. Among these factors are low temperatures, sodium derivatives of many organic and inorganic acids (sodium oxalate being more active than sodium citrate, sodium citrate more than nitrate and chloride and these more than tartrate, acetate and sulfate), cocaine chloride, zinc sulfate, novirudin and heparin.[5, 6] But it has not yet been possible to define by their physico-chemical properties how an opsonized surface differs from a non-opsonized one.[7]

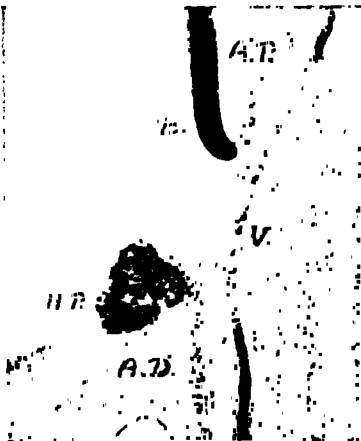


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This snapshot has been taken at the 10th min of the hemorrhage

On the other hand, a platelet seems to adhere to foreign surfaces by means of a protein film which always surrounds it. The nature and role of that protein layer are still mysterious.

When capillaries are cut, adhesion *of the endothelial cells to each other* often occurs and prevents bleeding. If that adhesion fails, capillary hemorrhage is then stopped by a coagulation of the blood similar to that occurring in vitro.[1, 2, 3, 4]

Nevertheless, extremely prolonged bleeding times are not observed in hemorrhagic diseases with basic plasmatic disorders such as hemophilia, hypoprothrombinemia, etc. On the contrary *very prolonged* bleeding *times are one of the most* important features of many purpuric patients with normal blood coagulation but with a low platelet count or with platelets deprived of their property to clump. Therefore, it has been said that purpura hemorrhagica is a platelet disease.

However, this is not entirely correct for it is possible to observe *very low platelet counts* without *any hemorrhagic* tendencies nor prolonged bleeding times. Moreover, in thrombocytopenia, as well as in purpura hemorrhagica with a normal platelet count, *both extremely prolonged and normal bleeding times have been recorded simultaneously but at different sites of the same organ* For instance, in a case of purpura hemorrhagica, bleeding times measured at the same time were 49 min at one place on the right ear and 4 min. at another place on the same ear In another case, these times were 48 min 30 sec at the right ear and 3 min. at the left one (see Fig 2)

This striking fact proves that profuse hemorrhages in such cases depend not only on a blood factor but also upon a *localized, peripheral, vascular one* [8]

The existence of this vascular factor is also shown by the study of hemostasis under the microscope. Using a modification of Chambers' and Zweifach's method, Hugues has observed in some cases a prompt piling up of platelets at one end either proximal or distal of a transected minute mesenteric artery or vein, while at the other end of the *same vessel* there was a

Bleeding time n° 1 48 min 30 sec (right ear).



Bleeding time n° 2 3 min (left ear)

Figure 2 Bleeding times measured at the same time but at different sites (right and left ears) in a case of chronic purpura hemorrhagica

greatly delayed formation of the hemostatic plug (see Fig. 1). The size of the aperture at each end was still identical. Therefore, this kind of prolonged bleeding time is apparently due to a located lack of opsonization.

COAGULATION OF THE BLOOD

As pointed out above, the microscopical study of hemostasis does not stress an important participation of the blood clotting process in this phenomenon. Nevertheless, the fact that blood coagulation plays a part in the arrest of bleeding is proved by the uncontrollable hemorrhage in hemophilia and hypothrombinemia. This is immediately stopped if the specific defect of the clotting mechanism is corrected.

Although striking advances have followed the numberless researches devoted to blood coagulation, the latter is still an enigma, for many active substances in this process have not yet been separated and purified.

Two diagrammatic representations conceived by W. H. Seegers[9] provide a summary of the chief factors acting in coagulation to which a co-factor V (or factor VII) apparently may be added (see Fig 3).

Some of the substances participating in blood clotting also play a great role in hemostasis The most important are (1) fibrinogen (diminished or absent in hypo- and afibrinogenemia); (2) prothrombin (reduced in hypoprothrombinemia), and (3) the Quick's labile factor, Owren's factor V or Seegers' plasma Acglobulin (diminished in Owren's disease).

The prolonged coagulation time in hemophilia is due to the lack of an anti-hemophilic globulin largely concentrated in fraction I and in fraction II plus III of the plasma proteins. The nature of this globulin is still unknown, but many investigators believe that it is related to thromboplastinogen.

The deficiency of the coagulation mechanism is rarely caused in man by a circulating anticoagulant, the nature of which is still obscure. In exceptional cases (exposure to ionizing

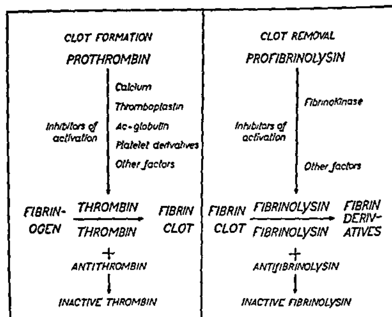


Figure 3. Diagrammatic representations of the blood clotting process

radiation), the inhibitor of clot formation seems to be heparin, a powerful anticoagulant. The latter is definitely liberated in dogs by either anaphylactic shock or injection of peptone.

Recently, attention has been drawn to the increased facilitation of clot removal by fibrinolysis in the pathogenesis of some hemorrhagic diseases. Certain investigators assert that fibrinolysis is distinct from the blood clotting process Others believe that it is due to a lytic property of thrombin on fibrin.

Anyhow, at the present time, very few experiments have been carried out to see *how* a defect in blood coagulation can intervene in hemostasis and therefore result in prolonged hemorrhage.

The main facts known about the arrest of bleeding in all these hemorrhagic disorders with disturbed clot formation are obtained from clinical information, i.e.: (1) associated with a prolonged coagulation or prothrombin time, there is a normal

or only slightly prolonged bleeding time. The hemorrhage however may start again after having ceased for a time; (2) true purpuric spots are absent and the tourniquet test is negative; (3) persistent hemorrhages generally follow a slight injury and are found at sites of the body which are exposed to repeated touches.

These features characterize many pathological states grouped under the name of "hemophilic syndromes" as opposed to "hemogenic syndromes." The latter include the hemorrhagic disorders with (1) normal blood coagulation but prolonged bleeding times, (2) presence of true purpuric spots and often a positive tourniquet test; (3) spontaneous and ubiquitous persistent hemorrhages.

Both syndromes represent what is called a "hemostatic paradox." Their association leads to complicated hemorrhagic disorders, the "hemophilo-hemogenic syndromes," which are often severe and which assemble symptoms of either syndrome.[20]

VASCULAR CONTRACTION

After two centuries of disagreement, the existence of vascular contraction following the cutting of an arteriole or of a venule has been proved. Apitz,[1] but chiefly Zucker,[2] Chen and Tsai[3] and Hugues[4] have observed that this vasoconstriction can only be seen when it is observed under incident light, as opposed to reflected light. These vascular contractions require also, in order to be established in mammals, the use of the Chambers' and Zweifachs' method[33] or of a similar one.[4]

Such a narrowing of minute vessels cannot be considered as a result of their crushing by the blade of a scalpel It does not depend upon the fall of the blood pressure either, but *is due to the contraction of vascular smooth muscle*

This is proved by the following facts· (1) the constriction disappears or decreases after the muscle fibers of the vessel have been paralysed by certain drugs such as benzene, Mg ions, nitrites, allylisothyocyanate,[4] (2) the length of the constricted

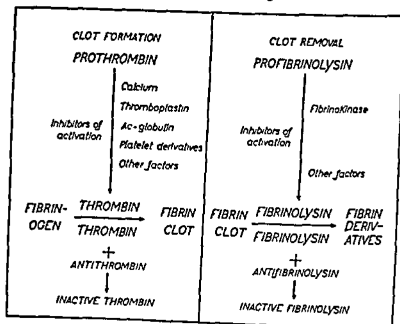


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as the speed of the blood flow, chemical properties of the vascular wound, etc. remain unchanged.

RECAPITULATION

The facts disclosed by the analytical study of spontaneous hemostasis have undoubtedly proved that:

1. The arrest of bleeding through minute vessels (small arteries and venules) depends upon the agglutination of blood platelets at the mouth of the vascular wound which leads to the formation of a white thrombus acting as a hemostatic plug;

2. The arrest of capillary bleeding (if such bleeding is not prevented by adherence of endothelial cells) depends upon a blood coagulation;

3 The firmness of the hemostatic plug which prevents a renewed bleeding, depends upon normal blood coagulability,

4. The injury of a minute vessel (arteriole or venule) results in a localized vasoconstriction, whose participation in spontaneous hemostasis is probable

In spite of the importance of the data supporting these conclusions, the mechanism of spontaneous hemostasis was still not entirely solved. Is this phenomenon modified in patients who require a prompt arrest of bleeding because of a great loss of blood? Is the deficiency of such a hemostatic factor in hemorrhagic disease sufficient to prolong indefinitely the bleeding of the patient? Does the administration of a coagulant or of a vasoconstrictor always favor spontaneous hemostasis?

Up to the present time, answers to such questions were hypothetical. An attempt to answer them on an experimental basis will be found in the following chapters.

segment sometimes reaches as much as 1-1,5mm. for a vessel, the diameter of which is only 40-80μ; (3) there is a close relation between the degree of the vascular narrowing and the richness of the vessel in muscle fibers; (4) the vasoconstriction occasionally appears moniliform, (5) one would expect after *section, an immediate narrowing of the blood vessel due to the* immediate localized fall of the blood pressure. However, this does not always take place at once because of the delayed contraction of the muscle fibers of the vessel; (6) vascular contraction infrequently persists even after hemorrhage has stopped.

As vasoconstriction following an injury is more pronounced if there are more muscle fibers in the vascular wall, then the narrowing of arteries is greater than that of veins.

As mentioned above, cut capillaries do not generally bleed, for their walls adhere to each other as do the walls of a fresh narrow rubber tube which has been cut with sharp scissors. A similar adherence may occur if the vessel is a rather small venule (diameter less than 30μ) cut with blunt scissors.

Do these contractions favor the arrest of bleeding?

In the Rendu-Osler-Weber disease, or hereditary hemorrhagic telangiectasia, which is a disorder characterized by a scattered dysplasia of the minute vessels, bleeding time is most frequently prolonged when telangiectasies are cut Its value is normal in the unaffected areas. The coagulation time, prothrombin time, clot retraction, platelet count and their adhesiveness as well as the tourniquet test are normal [10, 12] Observed with the help of a capillaroscope (using reflected light), the dilated and distorted minute vessels do not seem to contract when cut.[12]

Therefore, vasoconstriction seems a necessary part of hemostasis. *It was logical to suppose that all other factors being* equal, the closure of a vascular wound would be quicker if a vasoconstriction had reduced the diameter of the aperture. However, it is not known whether in these conditions such factors

longed by a high pH (i.e. 9). If the temperature of the running water is about 40°C, its length is at a minimum. The bleeding time increases if the temperature decreases, specially under 10°C and bleeding does not cease at all at temperature about 2°C (see Fig. 5). This has practical consequences, for it forbids—as we shall see later (see page 51)—the widespread use of cold (ice bags, icy drinks, etc.) in the treatment of hemoptysis, hematemesis, etc.

Other conditions must also be standardized. (1) the rabbit must be *non-anesthetized*, gently handled and immobilized; (2) its ear previously shaved and fixed without blood stasis; (3) bleeding time measured from the time of cutting until the moment when the hemorrhage has stopped bleeding for 30 sec.; etc.

BLEEDING TIME IN MAN BY A MODIFICATION OF DUKE'S TECHNIQUE[14]

According to the original Duke technique, bleeding time is measured at the lobe of the ear after it has been cut with a sharp scalpel. Every ½ min, blood escaping from the vessels is blotted with filter paper in such a way as not to touch the wound.

In order to increase the number of measurements, incisions are repeated twice at the lobe and three times at the helix of each ear, as shown in Figure 6.

BLEEDING TIME IN MAN BY DISHOEK'S AND JONGKEES' TECHNIQUE

Instead of cutting or stabbing the ear skin, Dishoek and Jongkees proposed to imitate an open wound. Therefore, they pressed the ear lobe against a thin steel plate with a circular opening 4mm. in diameter Then they cut off with a razor blade the small part of the lobe protruding through this hole. The plate is removed and the blood is sucked away every ½ min. by means of a filter paper (or cotton wool) without the wound being touched.

• 2 •

Techniques and Methods

THERE ARE many procedures for measuring the bleeding time. Three ways in which these techniques can differ are: (1) the instrument used for cutting or stabbing; (2) the way to avoid the persistence of blood on the wound so as to observe the end of the hemorrhage easily, (3) the organ which is injured.

Three among these procedures were chosen for the research presented here.

BLEEDING TIME IN THE RABBIT MEASURED UNDER RUNNING WATER [13]

In a first step, the minute vessels uniting the central and peripheral vessels of a rabbit's ear are cut with a sharp scalpel in 4mm. lengths, by groups of 5, in 4 definite areas (see Fig. 4).

After the cutting, the hemorrhage is observed under neutral running water (pH 6,8—7) at constant temperatures (about 28°C). *These points are very important for bleeding time* varies with them. It is shortened by a low pH (i.e. 5) and pro-

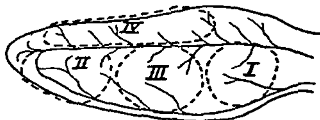


Figure 4 Areas where skin and underlying vessels were cut in order to measure bleeding times under running water in the rabbit



Figure 6. Areas where skin and underlying vessels were cut in order to measure bleeding times by means of modified Duke's technique in man.

ear, we shall see that there is a close correlation between the "mean bleeding times" of the right and left ears in every subject. The same close correlation has been observed between the mean bleeding times of both ears after 20 bleeding times have been measured at each ear under running water in the rabbit, or three at each ear by Dishoek's and Jongkees' technique in man (see Fig. 7).

Thus the mean bleeding time (i e., the average value of a statistically sufficient number of individual bleeding times measured in an experimental animal or in a man under standardized conditions) is nearly the same at each ear, provided that no factor had acted on the organism between the two series of determinations.

METHODS FOR STUDYING SPONTANEOUS HEMOSTASIS

In order to study the action of hemostatic agents, some investigators have compared the mean bleeding time of one group

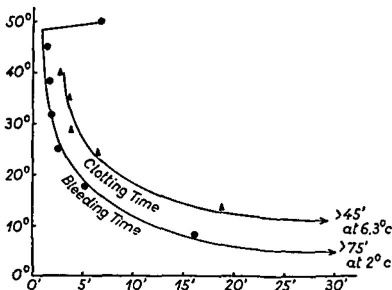


Figure 5 Bleeding and clotting times at different temperatures

To use Dishoek's and Jongkees' technique, Duesberg devised a forceps which may be employed in this method. With the help of this forceps, he successively measured three bleeding times at the lobe of each ear [15]

INDIVIDUAL AND MEAN BLEEDING TIMES

Measured under these conditions, a single bleeding time (which we therefore call the "individual bleeding time") is very variable indeed, even in normal subjects For instance, in a healthy rabbit normal individual bleeding times may range from 20 sec. to 9 min , in a normal man, from 30 sec to 4 min. 30 sec. (measured by modified Duke's technique), from 1 min to 5 min. 30 sec. (measured by Dishoek's and Jongkees' technique).

Let us measure in 50 men, five bleeding times for each ear by modified Duke's technique. Then, having calculated the average values of the individual bleeding times obtained at each

cause of this statistical inconsistency, it could not be used for the experimental study of spontaneous hemostasis [17]

Consequently, the method chosen for the researches presented here, has compared the control mean bleeding times and the modified ones *in the same subjects* If the modified (or experimental) mean bleeding time varies from the control by a factor of plus or minus 2,5 x the standard deviation, the difference is considered a significant one. This method led us to accurate results with the least expense of time and animals.

This was especially due to the use of certain "criteria of rejection," permitting a selection of the subjects for experimentation and of the results obtained.[13, 14, 15]

The crude results of our experiments and the statistically selected ones were in every case similar, but the accurateness of the latter was much greater. For instance, the average of 31 mean bleeding times in man decreased from 2 min 6 sec. to 1 min. 46 sec. after they were given 100 μg adrenoxyl. The use of the criteria of rejection reduced the number of these results employed from 31 to 21 and both average bleeding times from 2 min 6 sec. to 1 min. 50 sec and from 1 min 46 sec. to 1 min 26 sec. But Laplace's curves corresponding to the crude results and their standard deviation are superimposed (see Fig 8). In this case, the decrease of bleeding times might occur as a result of chance (1 10). The curves concerning the statistically selected results were much more distinct These results would be due to chance in only 1·400 times.[15]

These procedures for measuring bleeding time and the statistical methods for studying spontaneous hemostasis are discussed more fully elsewhere.[13, 14, 15, 18] To produce reliable information, they require trained investigators, meticulous attention and a perfect planning of the experiments in order to prevent unknown factors from interfering between the two series of determinations In our opinion, the importance of the question deserves such care

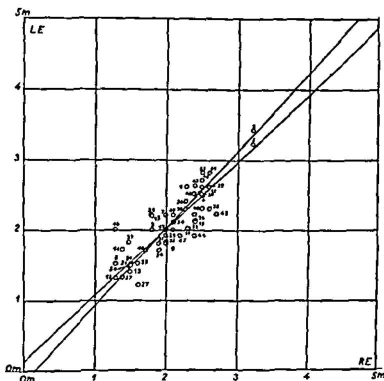


Figure 7 Correlation between mean bleeding times of both ears in 50 healthy men (Dishoek's and Jongkees' technique).
Ordinate: Bleeding times at the left ear, abscissa Bleeding times at the right ear

of mice to the mean bleeding time of another group which had been given some drug. In each animal, only a single bleeding time was measured at the tail.[16]

Such a method seems statistically faulty, because there may be great differences between two single bleeding times in the same mouse and even more in two different mice. Moreover, we have studied the standard deviation of 350 mean bleeding times, each value representing the average of 20 individual bleeding times measured at one ear in an untreated rabbit. The standard deviation thus obtained was much too large. Therefore, be-

• 3 •

The Physiological Study of Spontaneous Hemostasis

LOCAL VASOCONSTRICTION AND THE ARREST OF BLEEDING

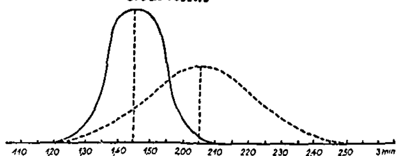
IT WAS pointed out above that a minute vessel contracts when it is cut. Is such a constriction useful for the arrest of bleeding? Experiments carried out on rabbits disclosed that: (1) stimulation of the distal end of a cut sympathetic chain in the neck leads to an important vasoconstriction of the corresponding ear and to a synchronous decrease of the bleeding time measured at the same ear, (2) on the contrary, superior cervical ganglionic sympathectomy brings forth ipsilateral vasodilatation and prolonged mean bleeding time (see Fig. 9). *This apparently means that local vasoconstriction in a given organ favors spontaneous hemostasis for that organ.*[19]

ADRENALINE AND MEAN BLEEDING TIME

These facts and the physiological importance of adrenaline in homeostasis raise the question as to whether this hormone also reduces the length of hemorrhage.

A dose of 10-25 μg of adrenaline pales the rabbit's ear and paradoxically prolongs the bleeding times when it is administered immediately before the cutting of the vessels[20] (see Fig. 10)

On the other hand, adrenaline is rapidly oxidized and thus inactivated in the organism Nevertheless, a very small dose (1 μg) of this amine which is unable to produce a generalized



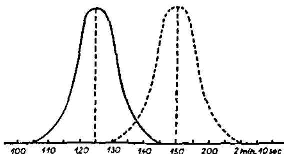


Figure 8 Crude and selected results of experiments showing the decrease of mean bleeding times by adrenoxyl Dotted curved lines: histograms before adrenoxyl, unbroken lines histograms after adrenoxyl

• 3 •

The Physiological Study of Spontaneous Hemostasis

LOCAL VASOCONSTRICTION AND THE ARREST OF BLEEDING

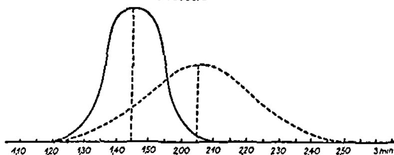
IT WAS pointed out above that a minute vessel contracts when it is cut. Is such a constriction useful for the arrest of bleeding? Experiments carried out on rabbits disclosed that: (1) stimulation of the distal end of a cut sympathetic chain in the neck leads to an important vasoconstriction of the corresponding ear and to a synchronous decrease of the bleeding time measured at the same ear; (2) on the contrary, superior cervical ganglionic sympathectomy brings forth ipsilateral vasodilatation and prolonged mean bleeding time (see Fig. 9). *This apparently means that local vasoconstriction in a given organ favors spontaneous hemostasis for that organ* [19]

ADRENALINE AND MEAN BLEEDING TIME

These facts and the physiological importance of adrenaline in homeostasis raise the question as to whether this hormone also reduces the length of hemorrhage.

A dose of 10-25 µg of adrenaline pales the rabbit's ear and paradoxically prolongs the bleeding times when it is administered immediately before the cutting of the vessels [20] (see Fig. 10)

On the other hand, adrenaline is rapidly oxidized and thus inactivated in the organism. Nevertheless, a very small dose (1 µg) of this amine which is unable to produce a generalized



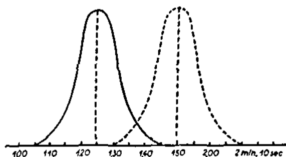


Figure 8 Crude and selected results of experiments showing the decrease of mean bleeding times by adrenoxyl Dotted curved lines. histograms before adrenoxyl, unbroken lines histograms after adrenoxyl

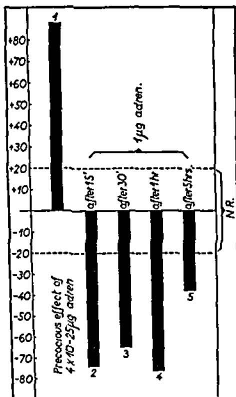


Figure 10 The effects of different doses of intravenous adrenaline hydrochloride on the mean bleeding time
Precocious effect (1) *of 4 injections 10 25 µg* of adrenaline hydrochloride, each preceding 5 cuttings Then, decreases of the mean bleeding time successively 15 (2) and 30 (3) min, 1 (4) and 6 (5) hrs after 1 µg of adrenaline hydrochloride has been injected

sympathicomimetic response, results in a reduced bleeding time, 15, 30, *60 min* and *even 6 hrs after its intravenous injection*[20] (see Fig 10).

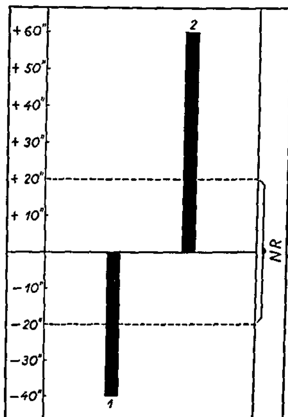


Figure 9 Effects of local sympathetic stimulation (1) and of localized ganglionic sympathectomy (2) on mean bleeding time

As other diagrams of this type in our monograph, this one represents by means of black rectangles the modifications of the mean bleeding time resulting from the action of various factors Depending upon whether they are above or below the horizontal axis, these rectangles show that the mean bleeding time is prolonged or reduced by the experimental factor The height of every rectangle shows the difference between the control mean bleeding time and the experimental one The space between both dotted lines corresponds to the normal range

In the upper diagram, rectangle 1 shows the decrease of the mean bleeding time due to ear vasoconstriction, rectangle 2 the increase due to vasodilatation.

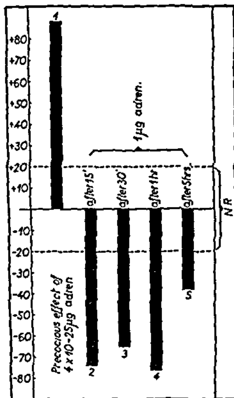


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sympathicomimetic response, results in a reduced bleeding time, 15, 30, 60 min and even 6 hrs. after its intravenous injection [20] (see Fig 10)

The sympathomimetic activity of adrenaline is closely related to the injected dose. Therefore, it is surprising to observe that its hemostatic action is not proportional to an increasing dosage between 0,01 and 10μg [21] (see Fig 11).

A number of experiments confirm and explain these paradoxical observations.

The Hemostatic Action of Oxidation Derivatives of Adrenaline

Oxidation of adrenaline gives birth to two substances with the subsequent formation of a blackish precipitate. One of them, called adrenochrome by Green and Richter and acting as an orthoquinone, was considered biologically inactive in the course of recent years. The other, discovered by Bacq and Heirman, hinders the stimulating activities of the sympathetic system. However, at a dose of 1 μg, both substances greatly reduce the mean bleeding time. This effect may be seen 15, 30 and 60 min. after their intravenous injection (see Fig. 12).

Such facts suggest that adrenaline favors spontaneous hemostasis only after being oxidized into adrenochrome or some related substance.[22]

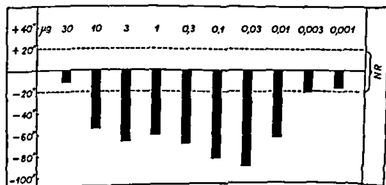


Figure 11. The hemostatic action of various doses of adrenaline hydrochloride in the rabbit 30 min. after injection.

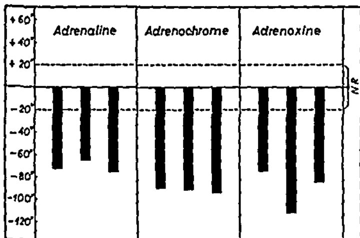


Figure 12 The hemostatic action of adrenaline hydrochloride and its oxidation derivatives
As in the Figure 14 (cardiazol), 19 and 20, each group of 3 series of experiments, corresponding to 3 grouped black rectangles, represents from the left to the right side the modifications of the mean bleeding time 15, 30 and 60 min after the drug has been injected

We attempted to confirm, or to invalidate, this hypothesis. Therefore, we devised a critical experiment which compared the bleeding times of three groups of rabbits measured at different intervals respectively before and after the administration of 1 μg adrenochrome, 1 μg adrenaline and 100 μg ephedrine.[23]

As shown in Figure 13, once the hemorrhage has *started*, these substances have no effect on its length But reduced bleeding times instantly *follow* the intravenous administration of adrenochrome On the contrary, a latent period, which is longer for ephedrine, precedes the hemostatic effects of both sympathicomimetic amines

Thus the long-lasting favorable action of adrenaline on the arrest of a future hemorrhage is apparently due to its oxidation to adrenochrome or to a closely related substance.

The Mechanism of the Hemostatic Action of Adrenochrome

How does adrenochrome shorten the bleeding time?

When the isolated amphibian heart [24] and rabbit's ear [25] are perfused with saline solution, an iterative stimulation of the corresponding sympathetic nerve results in a progressive disappearance of its cardioaccelerator and vasoconstrictor effect.

If adrenochrome or oxidized inactivated adrenaline are added to the saline solution, this disappearance of sympathetic activity cannot be obtained. In case the disappearance has already occurred, then this addition restores the normal effects of nerve stimulation. We supposed that the disappearance of these effects under the conditions just mentioned is due to the consumption of the "mother substance" of sympathin.

Since the hemostatic action of adrenaline is still observed in a denervated ear, *these experiments suggest that adrenochrome is stored at the endings of adrenergic nerves* (i.e., either at Cajal's interstitial meshwork or in muscle fibers) *and not in these nerves themselves.* Does it represent there a mother substance of the adrenergic chemical transmitter, a promediator which is transformed into sympathin by the vascular cutting and then causes vasoconstriction? Is the hemostatic action of adrenochrome related to its catalyzing properties? These possibilities are, up till now, only working hypotheses

HEMORRHAGE AND MEAN BLEEDING TIME

A moderately large hemorrhage causes (1) peripheral vasoconstriction; (2) an increased circulating platelet count; and *lastly* (3) hypercoagulability of the blood. Cannon's homeostatic theory emphasizes the adaptation of these responses to an useful end, i.e., an accelerated arrest of the bleeding. However, this is not entirely true.

In spite of these apparently favorable reactions due to an important discharge of adrenaline, the immediate effect of this discharge is the lengthening of the bleeding time. The greater

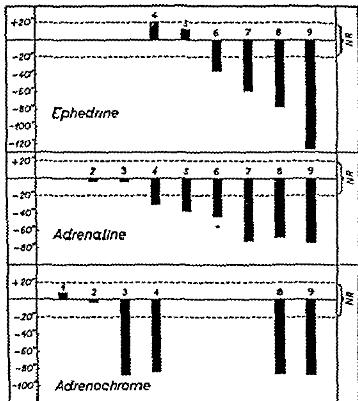


Figure 13 The latent period of the hemostatic action of ephedrine and adrenaline The absence of a latent period in the case of adrenochrome injection.
1 and 2 The skin was cut respectively 10 sec and immediately before drug injection, 3 the drug was injected immediately before the skin was cut, 4, 5, 6, 7, 8 and 9 the bleeding times were measured respectively 1, 2 5, 5, 10, 15 and 30 min after the drug was injected

the hemorrhage, the more prolonged the latter will be. However, if convulsions due to a very large hemorrhage occur, the bleeding time is instantly shortened[19] Bleeding time is also reduced after spasms induced by cardiazol This effect may be

caused by acid metabolites thereby produced, for a lowering of the pH decreases the bleeding time.

Thus the first effect of a hemorrhage is almost always an increased bleeding time due to an adrenaline discharge, but the secondary effect of this hypersecretion of adrenaline on spontaneous hemorrhage is usually favorable. For instance, the bleeding time measured 15, 30 and 60 minutes after the end of a hemorrhage is always shortened [26] (see Fig. 14).

THE EFFECTS OF ANESTHESIA ON MEAN BLEEDING TIME

It was asserted that a series of bleedings at one ear causes the mean bleeding time measured at the other ear to be

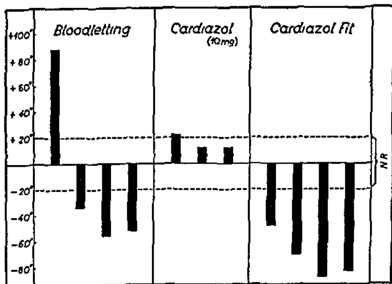


Figure 14 The modifications of the mean bleeding time after bloodletting (A), non-convulsiving (B) and convulsiving (C) cardiazol doses

From left to right, the black rectangles are related to the modifications of the mean bleeding time registered immediately (1), 15 (2), 30 (3) and 60 (4) min after the bloodletting or after the end of the cardiazol fit on one hand, 15 (1), 30 (2) and 60 (3) min after the injection of non-convulsiving doses of cardiazol on the other hand.

shortened. But, *this so called "post-traumatic shortening of the bleeding time" does not really exist. It has been observed solely in anesthetized rabbits and only because the anesthetic employed (urethane) produces a discharge of adrenaline.* This is proved by the effect of an intravenous injection of urethane which first prolongs the mean bleeding time (+ 69 sec.), subsequently shortening it when measured 45 min. later (— 78 sec.), thus mimicking adrenaline hypersecretion in a hemorrhage.[27]

Other anesthetics have been tested. Many of them modify the bleeding time, whereas others have no effect, as shown by the following figures (Table I,[28]).

Table I

Anesthetics	*Variations of the mean bleeding time from the control (normal range ± 20 sec.)* *Immediately*	*Tardily*
Chloralosane 10 cg/Kg i.-v.	— 14 sec.	— 1 sec
Dial Ciba 2,5 cg/Kg i.-v	+ 23 sec.	— 61 sec.
Narconumal Roche 2,5 cg/Kg i.-v	+ 1 sec.	— 53 sec.
Evipan Bayer 2,5 cg/Kg i.-v	— 16 sec	— 70 sec
Ethyl chloride	+ 23 sec	— 11 sec.
Chloroform	— 18 sec	— 26 sec.
Diethyl ether	+ 1 sec	+ 4 sec.
Methylal	+ 61 sec.	— 17 sec.

THE RELATIONSHIP OF HEPARIN AND VASCULAR CALIBER TO MEAN BLEEDING TIME

The bleeding time measured by Duke's method in men given large doses of heparin is similar to that of hemophiliacs, i.e., it is only slightly prolonged.

Experiments measuring the effects of heparin on rabbit bleeding time have an important bearing upon clinical problems.

1. The bleeding times of these animals are also only slightly prolonged by heparin if they are measured by the running water method, for, in this method, the ear is perfectly immobilized and the formation of the platelet plug is not im-

peded by constant movements or touchings (cf., bleeding times in hemophilia).

2. If the bleeding times are measured in rabbits by a method similar to that of Duke on man, the ear of the animal has to be unrolled between two fingers in order to permit the blotting of the blood. Then it cannot be perfectly immobilized and there are chances that the wound, which in this case has a tendency to open, would come in contact with the filter paper. Therefore, the bleeding time is more prolonged by heparin in these conditions (+ 3 min 34 sec), than if it is measured by the running water method (+ 50 sec).

If the bleeding time is measured by the running water method, it is prolonged by 86 sec. by a given dose of heparin, and by 60 sec. by the denervation of the ear One would expect that the lengthening of the bleeding time under the combined action of both factors would be 60 sec. + 86 sec. = 146 sec. However, under these conditions, the increase of the mean bleeding time is more than 12 min.[29]

In another series of researches, we devised many experiments on rabbits given gelatin, liquoïd and anti-blood platelet serum,[30] and thus demonstrated that very long bleeding times, such as seen in the hemogenic syndromes, require the combined action of a blood hemorrhagic factor and of a vascular one The above data prove anew the accuracy of our conception.

These results may be interpreted in terms of the Pharmacological Law of Burgi.[31] This law states that (1) when two drugs cause the same effect, both acting on the same pharmacological point of application, their combined action simply leads to the addition of their individual effects, (2) if their action bears on different pharmacological points of application, their *combined* action leads to "suradditive" effects, i.e., a result greater than the sum of their individual actions.

As proved by our results, this law also concerns pathogenic factors. *Thus the combined action of a blood factor* (hypoco-

agulability due to heparin) *and of a vascular one* (vasodilatation), *each having a slight individual increasing action on the bleeding time, leads to uncontrollable hemorrhages.*

THROMBIN AND THE MEAN BLEEDING TIME

After an operation or wound, small quantities of thrombin probably reach the circulating blood and are neutralized there by their combination with serum-albumine (metathrombin). Does thrombin modify the bleeding time before this neutralization occurs?

Experiments on the rabbit show that an intravenous injection of very small doses of thrombin (22 mg of "thrombine Roussel," or 88 μg of thrombin Parke-Davis, or 55 μg of thrombin Roche per Kg of rabbit) quickly reduces the bleeding time (— 31 sec. after 1 min) and has a prolonged effect (— 53 sec. and — 57 sec after 15 and 60 min.) Under these conditions, no thrombi are formed inside the vessels, and intravascular blood clotting or the disappearance of fibrinogen are not observed.

Therefore, thrombin may be injected in the muscles or even in the veins as a hemostatic agent, *provided the injected quantity is very small and the rate of injection very slow.* With large doses of thrombin, severe accidents may occur as was first observed by Mellanby in animals [82]

RECAPITULATION

The physiological use of the statistical method for studying spontaneous hemostasis has disclosed important facts.

1 Cannon's views about the maintenance of blood in mammalia [83] are not entirely correct

If adrenaline secretion has been enhanced by fear or anger, it certainly has the effect of shortening bleeding times when they are measured some time later. Convulsions following a large hemorrhage have also the effect of reducing the bleeding time. But one often sees a prolonged bleeding time when measured

immediately after a sudden hemorrhage. This is due to the immediate effect of a hypersecretion of adrenaline.

The "wisdom of the body" may be faulty. . . .

2. Such is not the case if thrombin is resorbed from a wound into the blood, for this enzyme shortens the bleeding time.

3. The hemostatic action of adrenaline presents particularities which raise the question of the role played by adrenochrome in the chemical transmission of adrenergic nervous impulses to automatic effectors.

4. Experiments with heparin give new proofs of the fact that extreme prolongation of the bleeding time, such as seen in hemogenic syndromes, depends upon the combined action of at least two hemorrhagic factors. The first is a vascular one. The second is related to disorder of the blood itself, hypocoagulability for instance.

These experiments also show the importance of mechanical factors in producing uncontrollable bleedings in hemophiliacs.

• 4 •

The Pharmacological Study of Hemostatic Agents

THE ACTION ON THE MEAN BLEEDING TIME OF DRUGS ALLEGED TO BE HEMOSTATIC

VASOCONSTRICTOR substances and drugs shortening the coagulation time were supposed to favor *ipso facto* the arrest of bleeding. In order to investigate this problem, the statistical method for studying spontaneous hemostasis was used and a number of so called hemostatic drugs were tested first on experimental animals[18, 20, 32, 34] and, some of them, later on men.[14, 25, 35, 36, 37]

The Effects of Blood Coagulants on Rabbit Bleeding Time

Among the substances reducing the coagulation time or supposed to have this property, are calcium salts, peptone 5%, gelatine 10%, the serum derivative called hemoplastin, the lung extract called clauden, the serum of sensitized animals called anthema and a spinal cord extract called manetol

The action of manetol on the rabbit bleeding time was found insignificant As shown in Figure 15, the former blood coagulants do not seem to favor the arrest of hemorrhage. Some of them even impede spontaneous hemostasis.

Nevertheless, other blood coagulants do reduce the bleeding time As mentioned before, this is the case with thrombin Two types of pectins (sangostop and coagucit), the platelet extract which is called coagulen and the cephalin which is derived from the latter (see Fig 16) also reduce the length of hemorrhage.

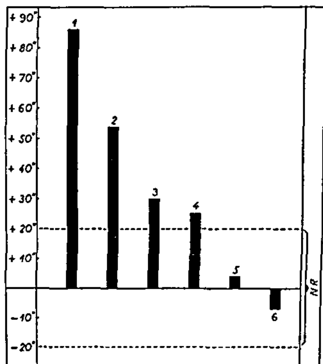


Figure 15. The effect on the rabbit mean bleeding time of different slowly injected hemostatics supposed to be coagulants.
From left to right: calcium glucono-galacto-gluconate (1), Witte's pepton 5% (2), gelatine 10% (3), hemoplastin (4), clauden (5), anthema (6).

Vasoconstrictor Substances and Rabbit Bleeding Time

In controlled conditions of time and dosage, spontaneous hemostasis is improved by some drugs supposed to be hemostatic because of their vasoconstrictor properties. These agents are adrenalone also called stryphnon, β-hypophamine also called pitressin and retropituitrin from which the latter is isolated (see Fig. 17).

However, a dose of two units of pitressin, though having vasoconstrictor properties, does not soon modify the bleeding

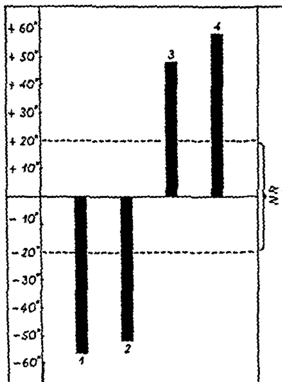


Figure 16 The effect of the platelet extract called coagulen and of various lipoids on rabbit mean bleeding time
From left to right, modifications of mean bleeding time 45 min after coagulen (1), cephalin extracted from coagulen (2), two samples of lecithin (3 and 4) have been injected

time in a significant way (+ 18 sec). This dose of the pituitary hormone shortens (— 40 and — 23 sec) the hemorrhage only 30 and 60 min after being given. In a similar way, a dose of 6 mg ephedrine injected intravenously prolongs (+ 64 sec) the bleeding time immediately. On the contrary, this is shortened when measured 30 min after its administration (— 50 sec).

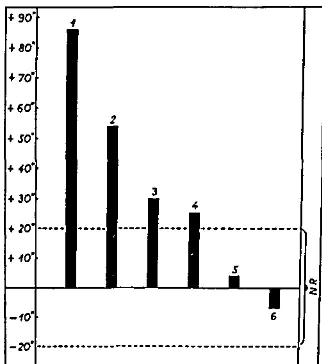


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A New Hemostatic Agent without Coagulating or Vasoconstrictor Properties

As pointed out before, adrenochrome, which was considered biologically inactive, reduces immediately and strongly the length of hemorrhages but only if it is administered *before* their onset.[22, 23]

But adrenochrome is rapidly oxidized in vitro and thus inactivated. In order to prevent this, stable derivatives of adrenochrome have been prepared. Among them are its monoxim and its monosemicarbazone Experiments on rabbit showed that both compounds have a similar but late hemostatic activity. The delay of the appearance of this activity depends upon the release of adrenochrome from these molecules.[35]

Experiments on Man Employing the Results Observed in the Rabbit

Many of these experiments carried out on the rabbit have been repeated on man The bleeding times were measured by the modified Duke's method and once by the Dishoek's and Jongkees' procedure. Thus the statistical method for studying spontaneous hemostasis in man confirmed the hemostatic action of coagulen,[36] sangostop [14] and stryphnon.[36]

It proved again that the bleeding time is not favorably modified after calcium galacto-gluconate or manetol have been injected However, men given 3 g calcium chloride per day for 1-3 days, present a slight decrease in the length of their hemorrhages [36]

These experiments also confirmed the hemostatic properties of some adrenochrome derivatives and allowed us to choose from among them the best for therapeutic use in man. Figure 18 shows that this is adrenochrome monosemicarbazone or adrenoxyl [15, 37]

Therefore, we may conclude that *a drug does not necessari favor spontaneous hemostasis even though it is a vasoconstrict or a blood coagulant.*

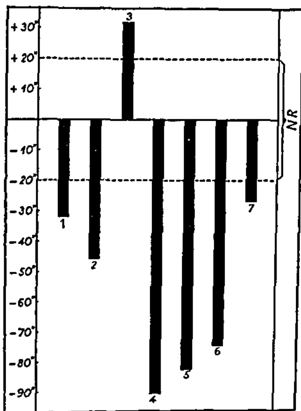


Figure 17. The effect on the rabbit mean bleeding *time of different hemostatics which are supposed to* be vasoconstrictor ones

Modifications of the mean bleeding time 10 min after whole retro-pituitary gland extract (1), pitressin (2), pitocin (3) *have been slowly intravenously injected.* Then its modification, 15 (4) and 30 (5) min, 1 (6) and 6 (7) hrs. after adrenalone (or stryphnon) has been administered.

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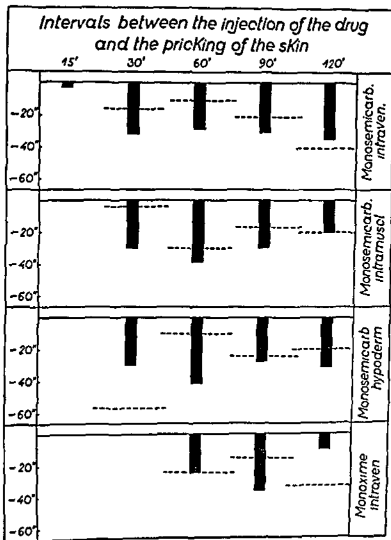


Figure 18. The hemostatic action of adrenochrome monosemicarbazone and monoxime in man at various intervals after their intravenous, intramuscular or hypodermical injection
Normal range dotted line

THE ACTION OF SYMPATHOMIMETIC AMINES NAPHTHOQUINONES, QUINONES AND SYMPATHOLYTIC SUBSTANCES ON MEAN BLEEDING TIME

Sympathomimetic Amines

For the most part, small doses of sympathomimetic amines shorten the bleeding time measured at the rabbit ear. Only 7 among 52 of them which have been tested, do not favor the arrest of hemorrhage.[20, 21, 34, 38]

An interesting fact has been observed concerning two of the most important of these active substances. The hemostatic action of adrenaline is apparently little changed by cocaine and by a sympathetic denervation of the ear. On the contrary, the action of ephedrine on the bleeding time is inhibited or even reversed by these two factors.

We must mention here a still controversial classification of the sympathomimetic amines which divides them into perfect

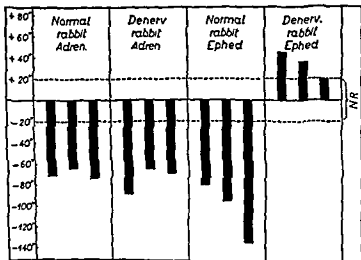


Figure 19 The hemostatic action of adrenaline and of ephedrine in the rabbit and their modification by a localized sympathectomy

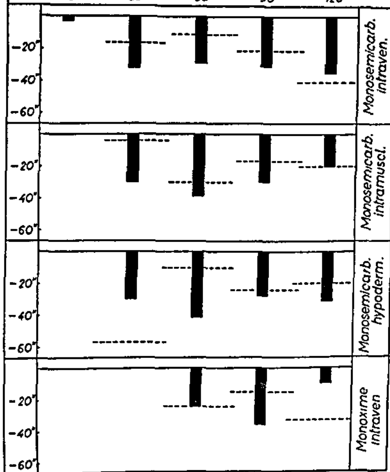


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Normal range. dotted line

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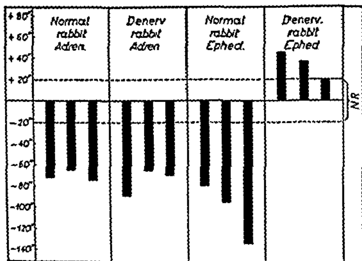


Figure 19 The hemostatic action of adrenaline and of ephedrine in the rabbit and their modification by a localized sympathectomy.

and imperfect sympathomimetics. The former are so called because (1) they accurately reproduce all the effects of stimulation of the sympathetic nervous system; (2) they act in this way on embryonic organs which have not yet received their sympathetic innervation and on organs denervated by ganglionectomy (see Fig. 19); (3) their action is sensitized by cocaine (see Fig. 20) and inhibited by ergotamin. The sympathomimetic amines having properties opposed to these are classified as imperfect sympathomimetic amines.

The basis of this classification may be criticized. Nevertheless, *a pharmacological study of the hemostatic properties of perfect and imperfect sympathomimetic amines confirms the existence of two such types of sympathomimetic hemostatic agents, some related to adrenaline* (perfect), *others to ephedrine* (imperfect).

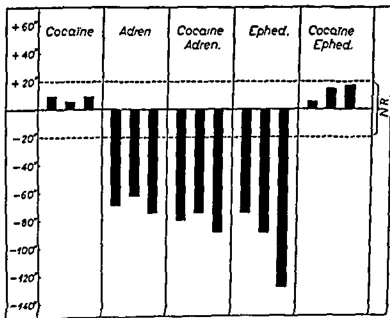
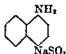


Figure 20. The hemostatic action of adrenaline and of ephedrine in the rabbit and their modification by cocaine.

This is supported by the relationship of certain structural modifications in the molecule of these amines to their hemostatic properties.[21, 34, 38, 39] For instance, the hemostatic properties of imperfect sympathomimetic amines are decreased with one hydroxyl group (OH) in position para or two hydroxyl groups in positions para and meta (see left part of Fig. 21). The opposite effect is observed in the case of perfect sympathomimetic amines (see right part of Fig. 21).

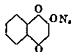
Naphthoquinones and Quinones

Other substances can also reduce the bleeding time. One of them is α-naphthylamine-4-sodium sulfonate:

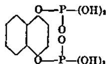


a derivative of Congo red. This was proposed as a hemostatic under the name of naphthionine S.N.S.[40]

The mean bleeding time is not modified 1 or 5 min. after S.N S. has been injected. Its hemostatic action is feeble 15 min. after injection It reaches its climax 30 and 60 min. after injection. This delay in the action of S.N.S is due to the time necessary for its oxidation in the organism Such an oxidation is required for the hemostatic action of S.N.S. For oxidized S N.S. as well as other quinones such as



and as a vitamin K-like substance, the synkavit



immediately reduce the length of hemorrhages.[41]

A latent period similar to those of adrenaline and of S.N.S. also precedes the hemostatic action of nearly all the diphenolic sympathomimetic amines. This period generally disappears in a similar way by the oxidation of the amines.[42]

and imperfect sympathomimetics. The former are so called because (1) they accurately reproduce all the effects of stimulation of the sympathetic nervous system; (2) they act in this way on embryonic organs which have not yet received their sympathetic innervation and on organs denervated by ganglionectomy (see Fig. 19); (3) their action is sensitized by cocaine (see Fig. 20) and inhibited by ergotamin. The sympathomimetic amines having properties opposed to these are classified as imperfect sympathomimetic amines.

The basis of this classification may be criticized. Nevertheless, *a pharmacological study of the hemostatic properties of perfect and imperfect sympathomimetic amines confirms the existence of two such types of sympathomimetic hemostatic agents, some related to adrenaline* (perfect), *others to ephedrine* (imperfect).

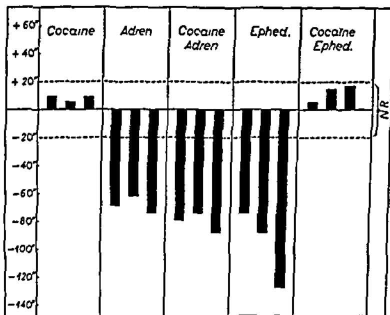


Figure 20. The hemostatic action of adrenaline and of ephedrine in the rabbit and their modification by cocaine

hydroquinone[41]] independent of the production of sympathin when a vessel is cut? These points are still controversial.

However, it must be remembered and emphasized here that: (1) local sympathetic stimulation always shortens the bleeding time, (2) the action of adrenaline (perfect sympathomimetic amine) on spontaneous hemostasis is still observed after cocaine and after ganglionectomy. On the contrary, these factors impair or even reverse the hemostatic action of ephedrine (imperfect sympathomimetic amine). Such phenomena are also observed for many other functions depending upon the sympathetic nervous system, i.e., contraction of the nictitating membrane, blood pressure, etc.

Sympatholytic Substances

It has been shown that relatively small doses of certain subtances impede the action of adrenaline. However, they do not inhibit the action of a sympathetic stimulation.

On the other hand, active doses of other substances regularly impede both the effects of adrenaline injection and of sympathetic stimulation.

The former substances, called adrenolytics, do not modify the bleeding time. On the contrary, the latter or sympatholytics regularly prolong the hemorrhages. Such are ergotamine, diethylaminomethylbenzodioxane, prosympal or 883F, allylaminomethylbenzodioxane or 993F, phenoxydimethylaminoethane or 407 J L. and o-methoxy-phenoxyethanolaminoethane or 416 J L[43]

These new pharmacological data are also an additional argument in favor of an important participation of the sympathetic nervous system in spontaneous hemostasis.

RECAPITULATION

The above facts may be summarized in a few main propositions

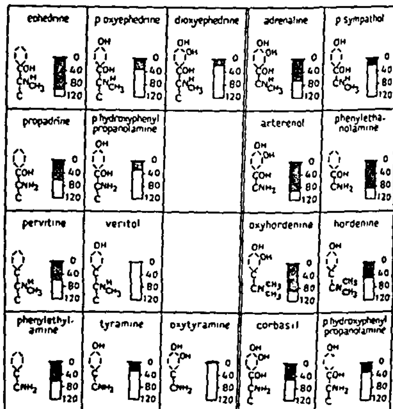


Figure 21. The influence of certain changes in the structural formula on hemostatic action of sympathomimetic amines
Each black rectangle corresponds to the average of the modifications of the mean bleeding time observed 15, 30 and 60 min after the intravenous injection of a dose of the experimented amine corresponding to adrenaline 1 μg

This seems to prove that the hemostatic property of these various compounds belongs to the quinonic structure.[41] Has the latter something to do with the postulated transformation of adrenochrome into sympathin (see page 24)? Or is the action of adrenochrome and of other quinones as well as of many phenols [phenol, catechol, hydroquinone, pyrogallol, hydroxy-

hydroquinone[41]] independent of the production of sympathin when a vessel is cut? These points are still controversial.

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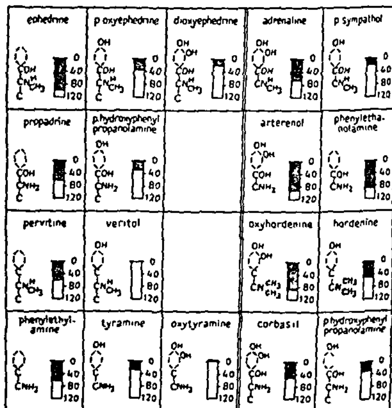


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• 5 •

Bleeding Time and the Detection of Hemorrhagic Diseases

IT IS NOT our purpose here to consider the various classifications of the hemorrhagic diseases and the basis of their diagnosis, nor to see how the bleeding time behaves in the different types of bleeders. It is to answer the questions: is the bleeding time test an important one in the detection of hemorrhagic diseases? What kind of information will it tell the clinicians? Two types of hemorrhagic disorders will be considered: (1) the hemorrhagic disease which is a major or severe one, or (2) the type in which the patient is a "minor bleeder" or is simply suspected of being a bleeder.

BLEEDING TIME IN THE MAJOR HEMORRHAGIC DISEASES

In the severe hemorrhagic diseases, the clinical picture, i e., history, physical signs and laboratory findings, generally leads to a precise diagnosis without measuring bleeding time. This test is then superfluous and could even be dangerous to the patient if it is much prolonged and the anemia pronounced [18, 44]

Therefore, in our opinion, the bleeding time test is not, as Quick [45] wrote, "exceedingly important in the diagnosis of haemorrhagic diseases." But what we have been taught by the study of the mean bleeding time has *a bearing upon our understanding of the severe hemorrhagic diseases, which must not be neglected*

1. Vasoconstrictor substances and coagulants do not *ipso facto* shorten the bleeding time. Some of them even prolong it in a significant way.

2. On the contrary, other drugs with the same fundamental properties favor the arrest of hemorrhage. These consequently are true hemostatics.

3. Other hemostatic substances seem to reduce the bleeding time by their quinonic functions, even if they are neither vasoconstrictors nor coagulants.

4. Adrenochrome which derives from the oxidation of adrenaline may be considered a physiological hemostatic.

Its action does not depend upon any vasomotor or clotting property. The question arises whether it is directly related to the formation of sympathin (for which it would be mother-substance) or if it is only due to its quinonic functions.

modifications of the local hemodynamics after the minute vessels have been injured, etc. The relative importance of these factors is not well known. However, it is proved that even a great deficiency in only one of them does not lead to an uncontrollable bleeding. The latter is caused by the failure of at least two factors.

Nowadays, a better understanding of the spontaneous hemostasis and of the pathogeny of the hemorrhagic diseases is needed. Further researches on everyone of the factors participating in the arrest of bleeding and on their co-operative action are necessary. This is more of a task for laboratory investigators than for clinicians

But clinicians also have their share in this work. In every case of hemorrhagic disease, they must try to evaluate all the abnormalities present in the patient. This has already been done by some clinicians For example, a lack of prothrombin has been occasionally found in anaphylactoid purpura which was supposed to be always due to a simple vascular defect [47] and purpura fulminans has been shown in some cases to be associated with a defect of Owren's factor V and with the presence of an heparinoid substance [48]

BLEEDING TIME IN THE MINOR OR LATENT HEMORRHAGIC DISEASES

Here the problem of the bleeding time presents itself in a different way.

The patient is not a major bleeder. He belongs to a family of minor bleeders or has himself shown frequent, but not profuse bleedings from nose or gums, etc., or had once presented a purpuric rash Let us suppose he must undergo an operation. Is he to be considered a bleeder or not? Must he then consequently receive special care in order to prevent postoperative hemorrhages?

Or let us suppose we deal with a patient bleeding from any organ, for instance from the meninges, uterus or digestive tract,

These diseases are characterized by extremely prolonged hemorrhages which are commonly asserted to be due to a simple vascular defect or only to a single definite blood abnormality such as thrombocytopenia, lack of platelet agglutination, decreased prothrombin activity, hypo- or afibrinogenemia, lack of antihemophilic globulin, heparinemia, etc.

We believe that such a concept of the hemorrhagic diseases is inaccurate, for a change in only one blood factor, such as a decrease in the circulating platelets, similar to that observed in thrombopenic bleeders, does not result in purpura hemorrhagica [46] nor in very prolonged mean bleeding times,[30] if this platelet defect remains the sole blood disorder.

In the same way, animals or men given large doses of heparin intravenously and whose blood is consequently uncoagulable, do not present a hemorrhagic disease nor greatly prolonged mean bleeding times if the other factors of hemostasis are normal. But, as already pointed out, the combined action of heparinemia and of sympathetic denervation severely impedes spontaneous hemostasis.[29]

These facts are important both in theory and practice.

As asserted by Quick,[45] knowledge concerning even the common hemorrhagic diseases is still incomplete. At the present time, intensive experimental work is concentrated on the important problem of blood coagulation Obviously, this trend of research has led to fundamental discoveries about hemorrhagic disorders. Nevertheless, blood clotting is not the same as spontaneous hemostasis and disturbances of the clotting mechanism are not the only factors involved in uncontrolled bleeding.

The spontaneous arrest of hemorrhage certainly depends upon blood clotting. But other factors also control the length of bleeding, i e., the number of circulating platelets, their ability to clump to foreign surfaces after these have been opsonized by plasma (or serum), the ability of the injured vessel walls to be opsonized by the plasma, the vasoconstriction, the

In Liège, the statistical study concerned 396 mean bleeding times in healthy people and 38 mean bleeding times in members of a family of minor bleeders (modified Duke's technique, 5 individual bleeding times for each mean one). The averages of both groups did not greatly differ from each other (1 min. 52 sec. in healthy people and 2 min. 8 sec. in people suspected of being or really being minor bleeders) and both histograms were also superimposable.

Our statistical criteria of rejection were applied to the two latter groups of bleeding times. Then great differences between them appeared For instance, only 5% of the mean bleeding times in the healthy people exceeded the length of 3 min. which is for us the limit of a normal mean bleeding time. This proportion rose to 16% in the people suspected of being or really being minor bleeders. Moreover, the difference between the mean bleeding times measured at the right and left ear was studied. A statistical method which assessed whether these differences were real or due to chance was employed. Thus the researches permitted to evaluate which figures would be valid.

In the healthy subjects, the deviation of the mean bleeding times between the two ears exceeded the statistical criterion of error in only 6,5% of the subjects. In the members of the family of minor bleeders, this deviation was observed in 52,6% of the patients, or in other words, a greater variability of bleeding times was found between the right and left ear of minor bleeders as opposed to normal subjects.[14, 51, 18]

In a special tourniquet test which we devised, a venous stasis in the forearm results from a pressure cuff placed on the upper-arm. The pressure employed is midway between the diastolic and the systolic pressure and is maintained for 15 min In the classical test, the number of the petechiae which appear in these conditions are counted and recorded. Moreover, in our technique, the sizes of the petechiae are measured In people without hemorrhagic tendencies, their diameter varies between 2/10 and 8/10 mm In the hemorrhagic diseases of the hemogenic

and it is not possible to discover the definite and local cause of these hemorrhages. Is then the patient to be considered a bleeder who requires a general treatment for his hemorrhagic tendency, or not?

To answer such questions, Duke devised his technique for measuring the bleeding time. He found that this was prolonged, usually very much so, in severe thrombopenic purpura hemorrhagica. He found it normal, and sometimes slightly or moderately prolonged, in the milder form of this disease. On the other hand, he asserted the bleeding time was normal in many other hemorrhagic diseases even with evidence of pathologic bleeding.[49]

Hoping to sensitize or to standardize the technique, many authors modified the tests as described by Duke. It can hardly be said that these modifications were improvements, for determining the hemorrhagic tendencies of a minor bleeder is more a statistical problem than a technical one. It should be noticed at any rate that. (1) the less severe the hemorrhagic disease is, the fewer will often be the abnormally prolonged bleeding times in a group of measurements; (2) however, the limit of the normal bleeding times varies with different investigators.

Recently, two series of statistical studies on bleeding times in healthy men and women as well as in people who were suspected of being or were really minor bleeders, have been made in Oxford[50] and in Liège[14, 51]

The first one concerned 98 mean bleeding times (6 individual bleeding times for each) in healthy people, and 205 mean bleeding times (3 individual ones for each) in people really being or suspected of being minor bleeders (technique of Ivy, Shapiro and Melnick). Oddly enough, the histograms of both groups of mean bleeding times were superimposable, and the average *of the mean bleeding times in healthy people* (5, 7 min.) exceeded the average of those in people being or suspected of being minor bleeders (4, 46 min.)!

· 6 ·

Prophylaxis and General Treatment of Hemorrhage

THE LOCAL medical treatment of bleeding has recently been the topic of the Seegers' and Sharp's monograph· *Hemostatic Agents.*[53] Their surgical handling is well known. Consequently, these special treatments will not be considered here.

The question this chapter will answer is: how can a hemorrhage be shortened or stopped without a direct handling of the minute bleeding vessels? The problem depends on whether the patient has a hemorrhagic disease with a well-known etiology or pathogeny.

PATIENTS WITH A HEMORRHAGIC DISEASE WHOSE ETIOLOGY OR PATHOGENY IS WELL KNOWN

If the causes of the hemorrhagic disease are known and can be successfully treated, prophylactic and curative treatments of the bleedings are often possible

For instance, hygienic conditions in factories, printing offices, etc., avert the hemogenic syndrome due to benzene intoxication Natural or synthetic vitamin C prevents scurvy. Vitamin K can cure some hypothrombinemias. B.A L. (British anti-lewisite) controls the hemorrhagic disease produced by gold or arsenic poisoning. Splenectomy generally heals chronic cases of thrombopenic purpura hemorrhagica These examples concern etiologic treatments.

In a similar way, many hemorrhagic diseases can be at least temporarily improved by treatments directed against the patho-

type (see page 9), their diameter reaches 1-3 mm. and the tourniquet test is then said to be qualitatively positive. As such, it has the same significance as a prolonged bleeding time.[82, 10]

In the family of minor bleeders just mentioned, there was some correlation between the hemorrhagic tendencies as revealed by the history of the patient and these two signs, i.e., abnormalities of the bleeding time and the qualitatively positive tourniquet test. This shows *the interest of a statistical study of a number of bleeding times measured in a person who is suspected of being or really is a minor bleeder.*

However, *the statistical study of bleeding time in minor bleeders or in people thought to be so, requires data carefully gathered by one skilful technician,* for the test varies with the investigators because everyone has his own way to prick the skin, to blot off the blood and to assess when the hemorrhage has ended.

RECAPITULATION

In our opinion, the bleeding time test is superfluous or even dangerous in the major hemorrhagic diseases. Its statistical study may be useful in people suspected of being or really being minor bleeders.

On the other hand, the study of spontaneous hemostasis as a whole reveals that uncontrollable bleeding depends upon more than one hemorrhagic factor. The clinician should be able to define these hemorrhagic factors in every type of hemorrhagic disease and in every bleeder as well.

is the case for hemorrhagic diseases whose etiology and pathogeny are well known and can be specifically treated. The efficaciousness of hemostatic treatments may then be established on a clinical basis.

However, this is not the rule. *One generally knows when a hemorrhage begins, but nobody can tell when it will stop. Thus, there is usually no clinical evidence of the precise activity of hemostatic medications.* Because of this lack of proof, wrong medications are often applied by clinicians on the basis of erroneous theoretical reasons. Also, they may have been prejudiced by cases in which the usage of these wrong medications was accidentally followed by a hemostasis (post hoc ergo propter hoc!).

So, according to the aphorisms of Hippocrates, one regularly applies low temperatures (ice bags, icy drinks, irrigations with icy water, etc.) to control hemorrhages (hemoptysis, hematemesis, melena, urinary bladder hematuria, encephalorrhagia, etc.), even in hemophiliacs.[45] In certain cases (uterine hemorrhage), warm temperatures (about 48-52°C) are preferred by some authors.

But, below the normal temperature of the mammals, and especially under 10°C, the lower the tissue temperature, the more prolonged are the bleedings. As we have observed it (see page 13), hemorrhage does not cease at a temperature of about 2°C Temperatures of about 50°C also impede spontaneous hemostasis. These facts have been found true not only of cutaneous, but also of visceral vessels.[54]

The hypothesis that visceral contractions due to the cold would locally favor spontaneous hemostasis lacks experimental evidence. Moreover, we have seen by means of x-ray examination that an icy opaque meal leads to gastroparesis and therefore cannot arrest the hemorrhage[54]

Thus the use of cold and heat in the treatment of the bleedings is not at all justified and should even be avoided in many cases because of its danger.

genic mechanisms. Thus transfusions ameliorate afibrinogenemia, hemophilia and Owren's disease because they correct the defect respectively of the blood fibrinogen, the antihemophilic globulin and Owren's factor V. Also hemogenic people with a low platelet count or with platelets deprived of their property to clump are improved if they receive normal platelets.

The prerequisite for the treatment of the pathogenesis of hemorrhagic diseases is an accurate knowledge of the hemostatic deficiencies involved. Such a knowledge is rather scarce. This emphasizes again the need of a better understanding of the various mechanisms of uncontrollable bleedings and, in every case, the necessity of a detailed exploration of the bleeder.

At the present time, the etiology and pathogeny of the hemorrhagic diseases are often imperfectly known. Therefore, an all-inclusive treatment of hemorrhage must be planned.

On the other hand, it happens frequently that the bleeding which has to be checked does not seem to depend upon a defect of general hemostatic factors, but on local hemorrhagic tendencies. In these cases also, the treatment to be applied is a general treatment for all the various types of hemorrhages, i.e., an "omnibus" one.

Similarly, before a surgeon begins an operation which exposes the patient to profuse bleedings (prostatectomy for instance) or which requires an especially perfect hemostasis (as cataract extraction), he wants to shorten any possible future hemorrhage. But, supposing the patient has no hemorrhagic disease, then what are the all-inclusive measures at the surgeon's disposal to improve spontaneous hemostasis in these cases?

PATIENTS WHOSE BLEEDINGS CANNOT BE SPECIFICALLY PREVENTED OR TREATED

Medications to be Rejected

In some special conditions, the application of a treatment almost always stops profuse bleedings in a very short time. This

5. Many blood coagulants, such as the blood platelet extract called coagulen, two pectins called sangostop and coagucit, and very small doses of thrombin (about 220 mg of thrombase, or 880 μg of thrombin Parke and Davis, or 550μg of thrombin Roche) reduce the length of bleeding if they are parenterally injected. The latter can improve spontaneous hemostasis even if its administration follows the hemorrhage.

It must be noted that pitressin can produce a state of shock, a rise of the blood pressure and contractions of the gastrointestinal tract. Therefore, it may be prescribed for hemoptysis and metrorrhagia with uterine inertia, but not in a case of hypertension or of gastro-intestinal hemorrhage. The other hemostatics are well tolerated This is true of parenterally injected thrombin provided that its dose is small. If it is injected intravenously, its administration must be slow (see page 29).

We used several of these hemostatics for prophylactic and curative treatment of hemorrhage when specific treatment was impossible or not sufficient.

Preventive Measures

As pointed out above, a prophylactic hemostatic treatment must be organized before every operation which exposes the patient to profuse bleedings or which requires a perfect hemostasis.

We always associate hemostatics acting on different pharmacological points of application, hoping to increase their effect in a suradditive way Thus we combine a vascular hemostatic (such as adrenoxyl, or stryphnon, or naphthionine S.N.S.), a coagulant (such as thrombin, or coagulen, or sangostop) and any calcium derivative (its mechanism of action still being unknown).

For instance, each patient receives a solution 4 g of calcium chloride by mouth, each day during the three days preceding the operation. Also the night before he is given an intramuscular injection of thrombase which is repeated an hour before the

Also, it was previously thought that bloodletting itself should be used in the treatment of encephalorrhagia. This is in agreement with Cannon's reasoning that a reduced bleeding time follows a moderate hemorrhage. However, in spite of the decreased blood pressure and its consequences (vasoconstriction, increased circulating platelet count and blood hypercoagulability), a moderately large hemorrhage is followed by a prolonged mean bleeding time (see page 24). Then this seems sufficient a reason to forbid bloodletting in encephalorrhagia.

Finally, we have found that many drugs acting as coagulants and as vasoconstrictors impede the spontaneous arrest of bleeding (see pages 31 and 33). In our opinion, this is sufficient evidence to give up their use as hemostatics.

Medications to be Retained

Here we will enumerate the drugs whose efficaciousness as hemostatics have been proved by accurate methods in experimental animals and in healthy men as well. We will also recall their main pharmacological characteristics.

1. The first one is the monosemicarbazone of adrenochrome, also called adrenoxyl. An injected dose of 100-500 μg shortens the mean bleeding time an hour after it has been administered but does not modify a hemorrhage which precedes its administration
2. The derivative of the Congo red called naphthionine S.N.S. and very small doses of nearly all the sympathomimetic amines (among them adrenalone, also called stryphnon) have a delayed hemostatic action on subsequent bleedings as well.
3. While parenterally injected, calcium derivatives impede spontaneous hemostasis, their action is favorable if they are administered by mouth.
4. An extremely slow intravenous injection of the retropituitary extract called pitressin or vasopressin (10-20 international units) seems clinically to shorten even a hemorrhage that preceded its administration.

rhages. In our opinion, there is also no other experimental method for studying the arrest of bleeding, up to this time.

Thus any hemorrhage can be treated with good chances for success, by drugs whose hemostatic properties have been experimentally established. Associating (1) a coagulant such as thrombin, coagulen or an active pectin; (2) a vasoconstrictor such as pitressin; and (3) calcium therapy, will probably lead to the greatest possible shortening of the bleeding time.

The use of hemostatics such as stryphnon and adrenoxyl to combat a hemorrhage is more questionable. They cannot reduce the bleeding time when they have been injected in healthy animals or men after the skin has been cut or pricked. Are they paradoxically beneficial to a bleeding patient? Some authors reported favorable observations after their administration. In our opinion, these are not significant and it is not proved that the vessels of an organ which is congested or inflamed behave otherwise than the vessels of the normal ear.

Comment

This might suggest a criticism to the reader. Our experiments have been done on rabbit's or man's ear. May their results be applied to the vessels of other organs?

The microscopical study of spontaneous hemostasis [1, 2, 3, 4] on several organs of various animals proved that the arrest of bleedings does not depend upon the mammalian species. It differs only according to the kind of vessel (artery, arteriole, vein, venule or capillary).

On the other hand, many pharmacological experiments on the rabbit's mesenteric vessels are, at the present time, in complete harmony with important facts statistically established on rabbit's and man's ear.[4]

These data plead for the use of only the medications which have been successfully tested by accurate methods in experimental animal and in man, as components of the "omnibus" hemostatic therapy of hemorrhage.

operation. The latter is associated with an injection of adrenoxyl, 500 μg. The results of such a treatment are generally good as shown by the following observation.

R. Fernand, a cachectic, 62 years old, was affected with alveolar pyorrhea and panmyelophtisis. His eight remaining teeth had to be pulled. Before the hemostatic treatment, after he had received three transfusions, the platelet count was 90 000 per mmc, the myelogram contained 75% lymphocytes, 1% normoerythroblast and no megakaryocyte. One bleeding time was stopped after 28 min. and the tourniquet test was qualitatively ++++++.

The eight teeth were pulled on April 9th, 11th, 17th, 20th and 23rd, each time after the prophylactic treatment described above. No excessive bleeding occurred though, on April 19th, *the platelet count was 40 000 and the tourniquet test was qualitatively* +++. However, the bleeding times were respectively reduced to 4 min, 8 min, 2 min 30 sec. at the right ear, and to 3 min. 30 sec., 3 min. 30 sec. and 4 min. 30 sec. at the left ear. The mean value was reduced to 4 min. 15 sec.

Curative Treatment

What is to be done for a patient when direct control of the bleeding vessels is impossible?

If his blood presents defects which can be corrected, they must be treated by the specific measures mentioned above. But, in such cases, it frequently occurs that the specific treatments are not sufficiently efficacious or that their effect is too delayed. Therefore, these hemorrhages, as well as those the etiology and pathogeny of which are unknown, require an "omnibus" medication.

In all these cases, the methods employed in the treatment of the patients are only on an experimental basis. The clue for this type of treatment is offered by our statistical study of hemostatics in healthy rabbits and men, because there is no clinical criterion for the efficaciousness of hemostatics in such hemor-

• 7 •

The Treatment of Thrombosis

THE FORMATION of a hemostatic plug after a vessel has been punctured or transected is useful. On the contrary, the intravascular agglutination of blood platelets to an injured endothelium is often dangerous. It can occur in an artery and produce a halt of the blood circulation in the corresponding part of the body, the importance of which is sometimes essential for health or even for life. If it happens in a vein, the thrombus too frequently becomes the remote origin of emboli, and these can cause severe diseases or sudden death.

Therefore, the discovery of a prophylactic and sometimes a curative treatment of thrombosis is one of the most striking advances in therapy in recent years This treatment consists in the use of drugs being anticoagulants or considered as such, for instance heparin and its substitutes or dicumarol and its derivatives. Their efficaciousness had been established in experimental animals [65] and in men.[66] But, how anticoagulants avert and even cure thrombosis was still a puzzle

HYPOTHESES ON THE MODE OF ACTION OF ANTICOAGULANTS IN THROMBOSIS

1. It might be supposed that anticoagulants could impede the "opsonization" of the injured vessel endothelium and consequently the agglutination of blood platelets to this surface and to each other at this site.

Such an explanation is inaccurate, for the concentrations of anticoagulants necessary to impede opsonization are much

RECAPITULATION

In hemorrhagic diseases, specific prophylaxis and specific treatment of bleeding consist essentially in averting or curing the causes of the illness and in correcting the blood deficiencies.

However, this is not always sufficient nor possible. Then an "omnibus" preventive and curative treatment can be employed as a result of the accurate statistical method for studying spontaneous hemostasis and of its application to the pharmacology of hemostatics. These treatments can be used to cure the bleedings of non-hemorrhagic patients as well.

Then, another phenomenon must prevent the growth of the thrombus. This is its tearing away by the blood, which has been microscopically seen and registered by moving pictures.

NEW MICROSCOPICAL OBSERVATIONS ON THROMBOSIS

The Very Beginning of Thrombus Formation in Normal Animals

If a small mesenteric artery or vein is damaged and no hemorrhage occurs, platelets adhere to the injured vessel wall and thereafter to each other.

Thus a platelet aggregate appears from which some agglutinated platelets are now and then torn away Nevertheless, the white thrombus becomes larger and larger and finally fills nearly all the diameter of the vessel. The larger the platelet aggregate is, the more energetically the blood stream beats against its extremity. Each pulsation shakes the whole white thrombus which is suddenly carried away by the blood stream as a micro-embolus and disappears

Immediately, the building up of a new thrombus begins again. As in preceding (and following) cases, it generally lasts for about 2-3 min. Frequently, this new thrombus is again torn away, another one taking its place. Such successive slow production of platelet aggregates and their repeated sudden dislodgment may last for half an hour, an hour or even more.[67]

This shows that a white thrombus is not easily formed because of the unfavorable action of the pulsatile blood stream. Experiments do not reveal that such small thrombi are stabilized by incorporating fibrin.

These facts suggest a new explanation for the prophylactic action of anticoagulants in thrombosis. As we have seen, large doses of these drugs prevent the opsonization of foreign surfaces and thus the adherence of platelets to them as well as to each other. Presumably, small doses hinder to a small extent

higher than those which hinder blood clotting and also than those which are found in the blood of the treated patients. An example: while the clotting of plasma is prevented for four hours by heparin 0,0025‰, heparin concentration of 5‰ is necessary to prevent the opsonization of yeasts by the plasma and their clumping to blood platelets. On the other hand, the usual daily dose of heparin for preventing a venous thrombosis in man leads to a blood concentration of the anticoagulant which is much less than 0,05‰.

Thus, the prevention of the opsonization of the vessel endothelium cannot be the sole mechanism used to explain the action of anticoagulants.[29] However, we will soon see that this may play a role in the dislodgment of the thrombus with small concentrations of anticoagulants.

2. Quick recently gave an explanation of thrombus formation and of the action of anticoagulants in combating thrombosis.[45] According to his views, the abnormality of the injured vascular endothelium induces the spreading of a thin layer of thrombin on the vessel wall. Consequently, the platelets adhere to this site (Step 1) Their subsequent disintegration liberates thromboplastinogen and thus causes a reticulated fibrin clot which enmeshes the intact platelets (Step 2). The retraction of this fibrin clot expresses a serum rich in nascent thrombin (Step 3). This produces a new fibrin coagulum which is attached to the tip of the primary thrombus (Step 4). Only such a growth by the successive formation of new clots and repeated expression of nascent thrombin by fibrin retraction would produce very long dangling and dangerous thrombi. Heparin could stop this growth because it inactivates thrombin and impedes the platelet disintegration

This mechanism is logical but rather hypothetical. It seems possible, even probable, if the thrombus is large enough. On the contrary, it does not seem to explain the very beginning of thrombus formation for, at this moment, there is no fibrin formation nor clot retraction.

Then, another phenomenon must prevent the growth of the thrombus. This is its tearing away by the blood, which has been microscopically seen and registered by moving pictures.

NEW MICROSCOPICAL OBSERVATIONS ON THROMBOSIS

The Very Beginning of Thrombus Formation in Normal Animals

If a small mesenteric artery or vein is damaged and no hemorrhage occurs, platelets adhere to the injured vessel wall and thereafter to each other.

Thus a platelet aggregate appears from which some agglutinated platelets are now and then torn away. Nevertheless, the white thrombus becomes larger and larger and finally fills nearly all the diameter of the vessel. The larger the platelet aggregate is, the more energetically the blood stream beats against its extremity. Each pulsation shakes the whole white thrombus which is suddenly carried away by the blood stream as a micro-embolus and disappears

Immediately, the building up of a new thrombus begins again. As in preceding (and following) cases, it generally lasts for about 2-3 min. Frequently, this new thrombus is again torn away, another one taking its place. Such successive slow production of platelet aggregates and their repeated sudden dislodgment may last for half an hour, an hour or even more.[87]

This shows that a white thrombus is not easily formed because of the unfavorable action of the pulsatile blood stream Experiments do not reveal that such small thrombi are stabilized by incorporating fibrin

These facts suggest a new explanation for the prophylactic action of anticoagulants in thrombosis As we have seen, large doses of these drugs prevent the opsonization of foreign surfaces and thus the adherence of platelets to them as well as to each other. Presumably, small doses hinder to a small extent

opsonization and platelet agglutination. But this feeble hindrance might become effective with the mechanical help of the beating blood stream. Thus, again, we see that more than one factor is necessary for a pronounced disturbance in blood homeostasis.

Locally Applied Anticoagulants and Their Relation to the Building Up of White Thrombi

Recent experimental data [58] are in agreement with these conclusions. They concern the local action of anticoagulants on the formation of a thrombus This was microscopically studied as small mesenteric vessels were washed by different solutions of anticoagulants before they were transected and then while they were bleeding.

Such experiments showed that (1) the concentrations of anticoagulants thoroughly preventing the formation of a hemorrhagic plug must be very high (heparin from 2,5 to 5%; sodium citrate 10%). They largely exceed the concentrations of the same substances needed to prevent blood coagulation; (2) heparin concentrations more than sufficient to prevent thrombo-embolic disease (0,025%) do not impede the formation of an apparently normal hemostatic plug; (3) hemostatic plugs which appear under washing by heparin 0,25% as well as by sodium citrate 0,5 and 1% look normal, but, nevertheless, cannot stop bleeding.[58]

Thus it is confirmed that these smaller therapeutic doses of anticoagulants cannot hinder the opsonization of injured vessel walls and thereby the agglutination of blood platelets to them. Even in normal animals, fibrin threads could never be detected in the *primary* platelet plug.[1, 2] It is then probable that fibrin plays no role in early thrombus formation in experimental animals or in men given therapeutic doses of heparin or dicumarol.

Therefore, *Quick's hypothetical explanation of the action* of anticoagulants in preventing thrombosis does not seem to be

accurate. Several authors [55, 59] assert that heparin, dicumarol and their substitutes appear to act by decreasing the platelet adhesiveness. Since the prerequisite of platelet agglutination is the opsonization of the foreign surfaces to which these corpuscles adhere,[5] it is probable that anticoagulants check the thrombus formation by at least partly hindrancing this opsonization.

Anyhow, their prophylactic action apparently depends upon *the increased fragility of the thrombus which consequently is more easily torn away from its insertion on the vascular wall.*

The mechanism of the curative treatment of thrombosis is more complicated This therapy has to deal both with opsonization and platelet agglutination, and with coagulation and clot retraction Anticoagulants can interfere with these processes upon which the thrombus propagation relies. But they also seem to favor fibrinolysis [60] and thus they may, in this way, hasten thrombus disappearance

THE PRACTICAL IMPORTANCE OF THE PRECEDING CONSIDERATIONS

Etiologic and pathogenic studies of thrombosis have shown that several factors are involved in its development. These factors are. (1) abnormalities of the inner surface of the vessel which can be caused by anoxia, infection, etc., and might exist even in the absence of any histologically demonstrable lesion,[61] (2) a localized or general slowing of the blood stream, (3) different modifications of the blood such as an increased platelet count, a lowered plasmatic albumin globulin ratio, an increased fibrinogen level, a hastened sedimentation rate of erythrocytes, etc

Before anticoagulants were introduced as preventive and curative treatments of thrombosis by Best, Jorpes and their collaborators,[55, 56, 62] prophylactic measures had been successfully used for combating thrombo-embolic disease. Great cares were taken not to damage the vessels, to avoid infections, but, above

all, to improve blood circulation, especially in the lower extremities.

Among the means employed to avert blood stasis were (1) foot and leg exercises in bed (sometimes with appropriate apparatuses); (2) deep breathing exercises; (3) avoidance of restriction to respiration or of postures slowing the venous circulation; (4) early ambulation of surgical and obstetrical cases; and (5) circulatory and respiratory analeptics. The results of these measures were extremely favorable.

In spite of this, they were frequently omitted in the prophylaxis of thrombosis after the usefulness of anticoagulants in thrombo-embolic disease had been published.

In our opinion, this is a mistake, for *thrombosis needs the synergistic collaboration of several disorders for its occurrence. Therefore, the best preventive and curative treatment of this disease must be a synergistic one. This is, in accordance with Burgi's law, hygienic conditions for the patients, perfect surgical techniques, measures improving the blood circulation, and the use of anticoagulants.*

RECAPITULATION

Microscopical studies in the rabbit of spontaneous hemostasis and of the experimental production of thrombosis have shown how a thrombus develops in the absence or even in the presence of anticoagulants.

On the basis of experimental evidence, the best prophylactic treatment of thrombosis appears to be a synergistic one which involves the combined action of (1) anticoagulants; and (2) measures deduced from the etiology of this disease. The chief aim of these measures is to improve blood circulation.

• 8 •

General Comments

DURING the last 70 years a number of first-rate researches were devoted to the analysis of every factor taking part in spontaneous hemostasis and, above all, to the study of blood clotting. Outstanding advances ensued. Nevertheless, all explanations of the arrest of bleeding considered as a whole were still speculative and unsatisfactory.

For instance, nobody could give the reason of what we termed the "hemostatic paradox" (see page 9), or tell why the bleeding time differs in a hemogenic patient according to the sites of pricking, and how very small doses of heparin prevent thrombo-embolic disease.

Our approach to the problem of hemostasis differed entirely from the preceding ones and we feel the experimental work in this field led to interesting results.

Our studies offered more than a clue in demonstrating the role of hemostatic factors in the arrest of bleeding and of their deficiencies in the pathogeny of hemorrhagic diseases. They have given an opportunity for studying the behavior of hemostasis in various physiological and pathological conditions. Also, they have been used to investigate the relationship of spontaneous hemostasis to homeostasis, to devise biological assays for hemostatics, etc

With their help, faulty hemostatic medications have already been discarded and new good ones discovered. Also, the synergistic use of several therapeutic measures has been planned to treat bleeding and thrombosis. These studies have shown

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Summary

HITHERTO, the arrest of bleeding, or spontaneous hemostasis, had been mainly studied in an analytical way. The present book results from an entirely new approach to the problem. Having observed that the "mean bleeding time" is a constant measurement in a subject under standardized conditions, the author devised a statistical method in order to study spontaneous hemostasis in experimental animals and men

With the help of this method, it is shown that Cannon's views about the maintenance of blood in mammals are not entirely correct The paradoxical effects of adrenaline (and consequently of bloodletting) as well as of many anesthetics on the bleeding time are explained The hemostatic action of thrombin is evidenced. Experiments with heparin give new proofs that extremely prolonged bleeding times depend upon the combined action of at least two hemorrhagic factors, one being vascular, the other consisting of some disorder of the blood itself.

Applied to pharmacological problems, the new method discloses that vasoconstrictor substances and coagulants do not ipso facto shorten the bleeding time. Some of these drugs even prolong it in a significant way On the contrary, other drugs with the same fundamental properties favor the arrest of hemorrhage The latter only may, consequently, be termed hemostatics. Other hemostatics seem to reduce the bleeding time by their quinonic functions even if they are neither vasoconstrictors nor coagulants Among new hemostatics thus discovered, is

that the pathogeny of hemorrhagic disorders as well as that of thrombo-embolism is a complex one, depending upon many blood and vascular factors.

Above all, a new statistical method for studying spontaneous hemostasis has been introduced, and this is based upon accurate measurements

Two statements are to be recalled here. Lord Kelvin wrote, "When you can measure what you are speaking about and express it in numbers, you know something about it," and Claude Bernard said, "An improved physiological experimentation consists not only in better instruments and procedures but, above all, in the logical and well controlled use of comparative experiments" (author's translation).

Therefore, we hope that the work exposed in this monograph on a statistical study of spontaneous hemostasis considered as a whole will inspire additional researches on this important subject

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adrenochrome (coming from the oxidation of adrenaline) which may be considered as a physiological hemostatic.

The bleeding time test appears to the author superfluous in the major hemorrhagic diseases. On the contrary, its statistical study may be very useful in the detection of minor or latent bleeders, especially of the "hemogenic type."

The new method for studying spontaneous hemostasis has more important consequences in therapeutics. It shows that wrong medications must be discarded; among them the widespread use of cold, heat, and bloodletting in the treatment of bleeding On the other hand, preventive and curative treatments result from pharmacological researches on bleeding time. These general treatments (as opposed to topical ones), are particularly intended for the hemorrhages which cannot be specifically or locally treated.

Finally, according to the facts disclosed by some of these experiments on bleeding time, and by microscopical studies on spontaneous hemostasis as well as on experimental thrombosis, the best prophylactic treatment of thrombo-embolism is shown to be a synergistic one, which unites the use of anticoagulants and measures improving the blood circulation

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Arrest of Bleeding

By

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